Direct Oral Anticoagulants: Determining Proper Use and Dose

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Target Audience: Pharmacists

ACPE#: 0202-0000-18-048-L01-P

Activity Type: Application-based
This activity is supported by independent educational grants from Boehringer Ingelheim Pharmaceuticals, Inc., and the Bristol-Myers Squibb and Pfizer Alliance.
Disclosures

Toby C. Trujillo, Pharm.D., BCPS-AQ Cardiology, FAHA, FCCP serves as a consultant for Janssen, CSL Behring, and Portola

Brent N. Reed, PharmD, BCPS-AQ Cardiology, FAHA has no relevant personal or financial disclosures.

The American Pharmacists Association is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.
Learning Objectives

1. Develop an evidence-based patient care plan for a patient requiring treatment with a direct oral anticoagulant (DOAC).
2. Identify patients who are at high-risk for adverse events associated with DOAC therapy and identify strategies for managing these patients.
3. Discuss strategies that optimize adherence and outcomes for patients receiving DOAC therapy.
Assessment Question 1

Which of the following would be an appropriate once-daily option in a patient with atrial fibrillation and normal renal function (creatinine clearance ≥ 120 mL/min)?

A. Apixaban
B. Dabigatran
C. Edoxaban
D. Rivaroxaban
Assessment Question 2

Which of the following is a modifiable patient-related barrier to adherence/persistence?

A. Socioeconomic status
B. Perceived benefits of therapy
C. Experience with treatment
D. Comorbid diseases/conditions
Assessment Question 3

Which of the following statements is true regarding the use of direct oral anticoagulants in the treatment of VTE?

A. Patients with a provoked proximal DVT or PE and at high risk of bleeding should receive extended anticoagulation to prevent recurrence

B. Patients receiving edoxaban for the management of DVT or PE should first receive 7 days of low molecular weight heparin therapy

C. Patients receiving apixaban for the management of DVT or PE should first receive 7 days of low molecular weight heparin therapy

D. Patients with a provoked proximal DVT or PE should receive anticoagulation for a minimum of 6 months
Assessment Question 4

Which of the following statements is true regarding the use of direct oral anticoagulants (DOACs)?

A. Patients who weigh > 100 kg should not be managed with DOACs

B. Compared to dalteparin, the use of rivaroxaban resulted in a lower rate of recurrent VTE in patients being treated for an acute VTE in the setting of cancer.

C. Patients with atrial fibrillation and receiving rivaroxaban along with concomitant therapy with phenytoin should have their dose increased to 15 mg BID

D. Patients on hemodialysis receiving apixaban 5 mg BID experience similar plasma drug concentrations as patients with normal renal function
Clinical Case BR – Resident in Assisted Living with PE

Presentation
- 85-year-old female
- Transferred from assisted living to ED with increasing SOB
- Fully ambulatory

Past Medical History
- Hyperlipidemia
- Hypertension
- Degenerative Joint Disease
- Hypothyroidism

Current Medications
- Atorvastatin
- Amlodipine
- Hydrochlorothiazide
- Levothyroxine

Physical Exam
- BP 140/78, P 80, R 14, PO2 94%, T 98.6, 50 kg
- Thin

Labs
- Normal CBC, PT, PTT, Cr 1.3, CrCl 46 mL/min, UA
- Normal CXR, ECG

Tests
- CTPA: Bilateral lower lobe single segmental defects
- Cardiac echo: No RV strain
What anticoagulant regimen is the best choice for BR’s initial treatment?

a. Apixaban 10 mg twice daily
b. Edoxaban 30 mg once daily
c. Rivaroxaban 15 mg once daily
d. Dabigatran 150 mg twice daily
e. All of the above are acceptable options
Growing Problem of Thromboembolic Events

VTE is a growing problem that results in significant negative outcomes.

AF, atrial fibrillation; VTE, venous thromboembolism

Limitations of Traditional Anticoagulation

- Warfarin only oral anticoagulant option for over 50 y\textsuperscript{1}
- Traditional anticoagulation (warfarin and/or parenteral anticoagulant to warfarin) suboptimal
  - Numerous limitations: narrow therapeutic window; need for frequent blood tests, dose adjustments; drug-drug interactions; drug-diet interactions\textsuperscript{2}
  - Recent registry data show suboptimal TTR in patients treated with warfarin\textsuperscript{3,4}
  - Registry data show practice subjective re: contraindications to warfarin; perceived benefit: risk not properly assessed\textsuperscript{5}
  - Adherence to guideline-recommended care suboptimal; persistence low\textsuperscript{6,7}
- These limitations put patients at risk for thromboembolic, bleeding events\textsuperscript{8}

TTR, time in therapeutic range

Recent Approvals Changed the Anticoagulation Landscape

- 6/8/1954: Warfarin approved
- 11/2/1963: JFK assassinated
- 7/20/1969: Neil Armstrong sets foot on the moon
- 11/9/1989: Berlin Wall falls
- 8/9/1974: President Nixon resigns
- 4/24/1990: Hubble telescope placed in orbit
- 10/19/1987: Black Monday
- 9/11/2001: Terrorist attacks on the Pentagon and WTC
- 8/29/2005: Hurricane Katrina
- 7/1/2011: Rivaroxaban approved
- 10/19/2010: Dabigatran approved
- 12/28/2012: Apixaban approved
- 1/8/2015: Edoxaban approved
- 6/23/2017: Betrixaban approved

- UFH and OAC used for PE 14-21 days in hospital
- UFH 7-10 days in hospital
- OAC begun day 1-2, 4-7 days in hospital
- LMWH outpatient treatment
Ideal Anticoagulant

<table>
<thead>
<tr>
<th>Disadvantage of Warfarin</th>
<th>Ideal Anticoagulant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow onset of action</td>
<td>Fast onset of action, allowing for acute treatment of VTE and use post-procedures</td>
</tr>
<tr>
<td>Need for injectable agent</td>
<td>Fast resolution of action, allowing for use peri-procedurally</td>
</tr>
<tr>
<td>Slow resolution of action</td>
<td>Fast resolution of action, allowing for use peri-procedurally</td>
</tr>
<tr>
<td>Routine blood monitoring</td>
<td>No routine blood monitoring</td>
</tr>
<tr>
<td>Many drug interactions</td>
<td>No drug interactions</td>
</tr>
<tr>
<td>Interactions with diet</td>
<td>No interactions with diet</td>
</tr>
<tr>
<td>Wide range of therapeutic doses</td>
<td>Narrow-range, fixed doses</td>
</tr>
<tr>
<td>Unpredictable dose-response</td>
<td>Predictable dose-response</td>
</tr>
<tr>
<td>Teratogenic</td>
<td>Safe in pregnancy</td>
</tr>
<tr>
<td>Slow reversibility via vitamin K</td>
<td>Immediate reversibility</td>
</tr>
</tbody>
</table>

No interactions organ dysfunction
# Direct Oral Anticoagulants (DOACs)

## Pharmacokinetics & Pharmacodynamics

<table>
<thead>
<tr>
<th>Property</th>
<th>Dabigatran</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Edoxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOA</strong></td>
<td>Direct IIa Inhibitor</td>
<td>Direct Xa Inhibitor</td>
<td>Direct Xa Inhibitor</td>
<td>Direct Xa Inhibitor</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>6 – 7%</td>
<td>80%</td>
<td>50%</td>
<td>62%</td>
</tr>
<tr>
<td><strong>Tmax</strong></td>
<td>1.5 hours</td>
<td>2 – 4 hours</td>
<td>2 – 3 hours</td>
<td>1 – 2 hours</td>
</tr>
<tr>
<td><strong>T½</strong></td>
<td>12 – 14 hours</td>
<td>9 – 13 hours</td>
<td>8 – 15 hours</td>
<td>8 – 11 hours</td>
</tr>
<tr>
<td><strong>Hepatic Metabolism</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>P-gp</td>
<td>P-gp</td>
<td>P-gp</td>
<td>P-gp</td>
</tr>
<tr>
<td></td>
<td>+ CYP3A4</td>
<td>+ CYP3A4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Protein Binding</strong></td>
<td>35%</td>
<td>90%</td>
<td>87%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>Dialyzable</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Measurement</strong></td>
<td>ECT, TT, aPTT</td>
<td>Anti-Xa, PT</td>
<td>Anti-Xa, dPT</td>
<td>Anti-Xa, PT</td>
</tr>
<tr>
<td><strong>Renal Elimination</strong></td>
<td>80%</td>
<td>35%</td>
<td>25%</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Renal Dosing</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>No?</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Antidote</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Source: J Am Coll Cardiol Intv 2014;7:1333–51
DOAC Selection in Venous Thromboembolism

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Venous Thromboembolism: The Third Leading Cause of Cardiovascular Death

- DVT: 2 million
  - Post-thrombotic syndrome: 800,000
  - PE: 600,000
    - Deaths: 60,000
  - Silent PE: 1 million
    - Pulmonary hypertension: 30,000

Estimated Cost of VTE Care in United States - $1.5 billion/year

U.S. Population-based VTE Trends

- 900,000 patients (1 to 2 per 1,000) afflicted with DVT or PE each year
- 60,000-100,000 Americans die of DVT or PE


**DVT** = deep vein thrombosis  
**PE** = pulmonary embolism
Indication | Recommendation (initial treatment) | ACCP Grade
--- | --- | ---
DVT or PE | LMWH (preferred, once daily) Intravenous UFH Fondaparinux (preferred) SC UFH • Oral VKA on day 1 or 2, minimum overlap 5 days, INR > 2.0 • LMWH preferred long term to new oral AC in patients not receiving VKA | 1B
Duration | • Provoked (surgical or nonsurgical, proximal or distal): 3 months over a shorter or longer duration • Unprovoked, first episode: 3 months, consider long term therapy • Unprovoked, second episode: long term preferred unless high bleeding risk | 1B 1B, 2B

Phases of Treatment for VTE

Initiation (5-21 days)
- UFH, LMWH, fondaparinux
- Rivaroxaban 15 mg BID
- Apixaban 10 mg BID

Early Maintenance (3-6 months)
- Warfarin (INR 2.0-3.0)
- Rivaroxaban 20 mg daily
- Apixaban 5 mg BID
- Dabigatran 150 mg BID
- Edoxaban 60 mg daily

Extension (up to indefinite)
- Warfarin (INR 2.0-3.0)
- Rivaroxaban 20 mg daily
- Rivaroxaban 10 mg daily
- Apixaban 2.5 mg BID
- Dabigatran 150 mg BID
- Warfarin (INR 1.5-2.0)
- Aspirin 81 mg daily

Acute VTE Treatment Options

- UFH = unfractionated heparin
- LMWH = low-molecular-weight heparin or fondaparinux
- VKA = vitamin K antagonists

Conventional VTE Treatment

- LMWH or UFH + VKA (overlap)
- VKA

Dabigatran

- Day 1
- LMWH

- Switching - Day 6-11
- Dabigatran 150 mg BID

Rivaroxaban

- Day 1
- Rivaroxaban 15 mg BID x 3 wk, then 20 mg daily

Apixaban

- Rivaroxaban 10 mg BID x 1 wk, then 5 mg BID

Switching - Day 6-11

- At least 3 months

**Length of Anticoagulation Treatment in VTE**

<table>
<thead>
<tr>
<th>Type of VTE</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provoked proximal DVT of leg or PE</td>
<td>3 months</td>
</tr>
<tr>
<td>Provoked isolated distal DVT of leg</td>
<td>3 months</td>
</tr>
<tr>
<td>Unprovoked DVT of leg (isolated distal or proximal) or PE</td>
<td>At least 3 months*</td>
</tr>
<tr>
<td></td>
<td>(1B recommendation over shorter duration)</td>
</tr>
<tr>
<td>1st VTE that is unprovoked proximal DVT of leg or PE and low/moderate bleeding risk</td>
<td>Extended†</td>
</tr>
<tr>
<td>1st VTE that is unprovoked proximal DVT of leg or PE and high bleeding risk</td>
<td>3 months</td>
</tr>
<tr>
<td>2nd unprovoked VTE in low/moderate bleeding risk</td>
<td>Extended†</td>
</tr>
<tr>
<td>2nd unprovoked VTE in high bleeding risk</td>
<td>3 months</td>
</tr>
<tr>
<td>DVT of the leg or PE and active cancer</td>
<td>Extended†</td>
</tr>
</tbody>
</table>

* After 3 months of treatment, evaluate for risk-benefit of extended therapy.
† Continued anticoagulant use should be evaluated at periodic intervals.

Patients with VTE and DOACs: Outcomes


- 39% lower major bleeding
- 64% lower fatal bleeding
- 63% less intracranial hemorrhage vs. vitamin K antagonists
Risk of Recurrent DVT/PE Persists Following Discontinuation of Anticoagulation

Patients with a first episode of clinically symptomatic proximal DVT and/or PE (N=1626)

Average of 6 months of anticoagulation treatment

Patients discontinued anticoagulation and were followed for recurrent DVT/PE

Role of Prevention of Recurrent VTE

Cumulative Incidence of Recurrent Thromboembolism by VTE Type

- Provoked
- Unprovoked

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Recurrent VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PREVENT</td>
<td>Warfarin, INR 1.5-2 vs. placebo</td>
<td>↓64%</td>
</tr>
<tr>
<td>ELATE</td>
<td>Warfarin, INR 2-3 vs. INR 1.5-2</td>
<td>↓63%</td>
</tr>
<tr>
<td>RE-MEDY</td>
<td>Dabigatran vs. warfarin, INR 2-3</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>INSPIRE</td>
<td>Aspirin vs. placebo</td>
<td>↓32%</td>
</tr>
</tbody>
</table>

Extended VTE Treatment & DOACs: Outcomes

Meta-analysis (n=3,015)

Recurrent VTE, VTE-related Death

EINSTEIN-EXT 0.20
AMPLIFY-EXT 2.5 mg 0.19 (0.09-1.40) 0.19 (0.11-0.33) 0.19 (0.11-0.34) 0.08 (0.03-0.27) 0.03 (0.00-0.49) 0.17 (0.12-0.24) 0.19 (0.09-1.40) 0.32 0.352 0.081 0.014 1.0

Fixed Effect 0.17 (0.12-0.24) 1.0

HR (95% CI)   W(fixed)

W = warfarin

• 83% relative risk reduction of recurrent VTE or VTE-related death (CI: 0.12-0.24, p<0.0001)


Major Bleeding

EINSTEIN-EXT 0.19 (0.09-1.40) 0.88 (0.48-154.5) 0.131
AMPLIFY-EXT 2.5 mg 0.19 (0.11-0.33) 0.49 (0.09-2.69) 0.388
AMPLIFY-EXT 5.0 mg 0.20 (0.11-0.34) 0.25 (0.30-2.28) 0.232
RE-SONATE 0.08 (0.03-0.27) 4.86 (0.23-101.1) 0.121
Kearon 1999 0.03 (0.00-0.49) 7.35 (0.39-140.1) 0.128

Fixed Effect 1.15 (0.44-3.31) 1.0

HR (95% CI)   W(fixed)

• No significant increase in the risk of major bleeding (CI: 0.40-3.31, p=0.38)
## Prescribing Information Highlights: Indications

<table>
<thead>
<tr>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of DVT, PE</td>
<td>Treatment of DVT, PE following 5-10 days of initial therapy with a parenteral anticoagulant</td>
<td>Treatment of DVT, PE in patients who have been treated with a parenteral anticoagulant for 5-10 days</td>
<td>Treatment of DVT, PE Take tablets with food</td>
</tr>
<tr>
<td><strong>Reduction in risk of recurrence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction in risk of recurrence of DVT, PE in patients who have been previously treated</td>
<td>Reduction in risk of recurrent DVT, PE following initial therapy</td>
<td>Not indicated</td>
<td>Reduction in risk of recurrence of DVT, PE Take tablets with food</td>
</tr>
</tbody>
</table>

Pradaxa (dabigatran etexilate mesylate) prescribing information. 2015 Nov.
Xarelto (rivaroxaban) prescribing information. 2016 Aug.
Eliquis (apixaban) prescribing information. 2016 Jul.
Savaysa (edoxaban) [prescribing information. 2016 Sep.
### Prescribing Information Highlights: Dosing

<table>
<thead>
<tr>
<th></th>
<th>Apixaban</th>
<th>Dabigatran</th>
<th>Edoxaban</th>
<th>Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg orally BID for 7 days, followed by 5 mg orally BID</td>
<td>10 mg orally BID for 7 days, followed by 5 mg orally BID</td>
<td>10 mg orally BID for 7 days, followed by 5 mg orally BID</td>
<td>10 mg orally BID for 7 days, followed by 5 mg orally BID</td>
<td>10 mg orally BID for 7 days, followed by 5 mg orally BID</td>
</tr>
<tr>
<td>If CrCl &gt;30 mL/min: 150 mg orally, BID after 5-10 day parenteral anticoagulation</td>
<td>60 mg daily</td>
<td>15 mg orally BID with food for first 21 days</td>
<td>15 mg orally BID with food for first 21 days</td>
<td>15 mg orally BID with food for first 21 days</td>
</tr>
<tr>
<td>• 60 mg daily</td>
<td>• 30 mg day if CrCl 15-50 mL/min, body weight ≤60 kg, or who use certain P-gp inhibitors</td>
<td>15 mg orally BID with food for first 21 days for initial treatment of acute DVT, PE</td>
<td>15 mg orally BID with food for first 21 days for initial treatment of acute DVT, PE</td>
<td>15 mg orally BID with food for first 21 days for initial treatment of acute DVT, PE</td>
</tr>
<tr>
<td><strong>Reduction in risk of recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.5 mg orally BID</td>
<td>If CrCl &gt;30 mL/min: 150 mg orally, BID after previous treatment</td>
<td>Not indicated</td>
<td>After initial treatment period, 20 mg orally daily with food for remaining treatment, long-term reduction in risk of recurrence</td>
<td>After initial treatment period, 20 mg orally daily with food for remaining treatment, long-term reduction in risk of recurrence</td>
</tr>
</tbody>
</table>

Pradaxa (dabigatran etexilate mesylate) prescribing information. 2015 Nov.
Xarelto (rivaroxaban) prescribing information. 2016 Aug.
Eliquis (apixaban) prescribing information. 2016 Jul.
Savaysa (edoxaban) [prescribing information. 2016 Sep.
Are the Direct Oral Anticoagulants First Line?

“In the absence of direct comparisons between DOACs ... no preference for one DOAC over another DOAC.”

DOAC Selection in Atrial Fibrillation

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Associate Professor
University of Maryland School of Pharmacy
Clinical Specialist – Advanced Heart Failure
University of Maryland Medical Center
Baltimore, MD
Patient Case

You must develop an anticoagulation plan for a 72 year-old woman with newly diagnosed atrial fibrillation. She also has HFpEF, HTN, CKD, and hypothyroidism. She weighs 68 kg and has a SCr of 2.2 mg/dL (CrCl 25 mL/min). All other labs are within normal limits.

Which of the following would be an appropriate DOAC regimen? Select all that apply.

A. Apixaban 5 mg twice daily
B. Dabigatran 150 mg twice daily
C. Edoxaban 60 mg once daily
D. Rivaroxaban 15 mg daily with evening meal

Home Medications
- Diltiazem 120 mg daily (new)
- Lisinopril/HCTZ 20/25 mg daily
- Levothyroxine 88 mcg daily

CKD chronic kidney disease, CrCl creatinine clearance, DOAC direct-acting oral anticoagulant, HCTZ hydrochlorothiazide, HFpEF heart failure with preserved ejection fraction, HTN hypertension, SCr serum creatinine
Atrial Fibrillation By the Numbers

*Therapeutics discussion to focus on nonvalvular atrial fibrillation (NVAF)*

- Approximately 6 million patients in the US have AF
- Estimated prevalence expected to exceed 12 million by 2030
- Atrial fibrillation increases the overall risk of stroke by 5-fold

CHA$_2$DS$_2$-VASc Risk Stratification Score

- **C** Chronic heart failure (1 point)
- **H** Hypertension (1 point)
- **A$_2$** Age $\geq$ 75 years (2 points)
- **D** Diabetes mellitus (1 point)
- **S$_2$** Stroke or TIA (2 points)
- **V** Vascular disease (1 point)
- **A** Age 65-74 years (1 point)
- **Sc** Sex category (women get 1 point)

TIA transient ischemic attack
Antithrombotic Therapy Selection

**CHA$_2$DS$_2$-VASc Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk of Stroke / Systemic Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Less than half of eligible patients are prescribed an oral anticoagulant.(^2)</td>
</tr>
<tr>
<td>1</td>
<td>Omit therapy (Class IIa, Level of Evidence B)</td>
</tr>
<tr>
<td>2</td>
<td>Aspirin, anticoagulant, or omit therapy (Class IIb, Level of Evidence C)</td>
</tr>
<tr>
<td>3</td>
<td>Oral Anticoagulation: Warfarin (Class I, Level of Evidence A)</td>
</tr>
<tr>
<td>4</td>
<td>DOAC (Class I, Level of Evidence B)</td>
</tr>
<tr>
<td>5</td>
<td>Warfarin (Class I, Level of Evidence A)</td>
</tr>
<tr>
<td>6</td>
<td>DOAC (Class I, Level of Evidence B)</td>
</tr>
<tr>
<td>7</td>
<td>Warfarin (Class I, Level of Evidence A)</td>
</tr>
<tr>
<td>8</td>
<td>DOAC (Class I, Level of Evidence B)</td>
</tr>
<tr>
<td>9</td>
<td>Warfarin (Class I, Level of Evidence A)</td>
</tr>
</tbody>
</table>

DOAC direct-acting oral anticoagulant

DOAC Prescribing Trends in Atrial Fibrillation

DOACs represent nearly half of all anticoagulants prescribed for atrial fibrillation

DOAC direct-acting oral anticoagulant
## DOACs versus Warfarin in NVAF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Apixaban (Eliquis®)</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Edoxaban (Savaysa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landmark Trial</td>
<td>ARISTOTLE¹</td>
<td>RE-LY²</td>
<td>ENGAGE AF³</td>
<td>ROCKET-AF⁴</td>
</tr>
<tr>
<td>Major Inclusion</td>
<td>≥ 1 stroke risk factor</td>
<td>≥ 1 stroke risk factor</td>
<td>CHADS₂ ≥ 2</td>
<td>≥ 2 stroke risk factors</td>
</tr>
<tr>
<td>Exclusions for Renal Impairment</td>
<td>SCr &gt; 2.5 or CrCl &lt; 25 mL/min</td>
<td>&lt; 30 mL/min</td>
<td>&lt; 30 mL/min</td>
<td>&lt; 30 mL/min</td>
</tr>
<tr>
<td>Mean CHADS₂ Score</td>
<td>2.1</td>
<td>2.1</td>
<td>2.8</td>
<td>3.5</td>
</tr>
<tr>
<td>Warfarin Mean TTR</td>
<td>66%</td>
<td>64%</td>
<td>68%</td>
<td>55%</td>
</tr>
<tr>
<td>Overall Efficacy</td>
<td>Superior</td>
<td>Superior*</td>
<td>Non-inferior†</td>
<td>Non-inferior</td>
</tr>
<tr>
<td>Overall Safety</td>
<td>Superior</td>
<td>Similar*</td>
<td>Superior</td>
<td>Similar</td>
</tr>
<tr>
<td>Other Notable Outcomes</td>
<td>↓ ICH</td>
<td>↓ ICH</td>
<td>↓ ICH</td>
<td>↓ ICH</td>
</tr>
<tr>
<td></td>
<td>↑ GIB*</td>
<td></td>
<td>↑ GIB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ fatal bleeding</td>
<td></td>
<td>↓ fatal bleeding</td>
<td></td>
</tr>
</tbody>
</table>

DOAC Dose-Selection and Outcomes in NVAF

Baseline Dosing

- Recommended Dose: 87.0%
- Over-Dosed: 3.4%
- Under-Dosed: 9.4%

Outcomes

- Major Bleeding: p = NS
- CV Hospitalization: p = 0.005
- Mortality: p = 0.04 for over-dose

CV cardiovascular, DOAC direct-acting oral anticoagulant, NVAF nonvalvular atrial fibrillation

## DOAC Dose-Selection in NVAF

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Apixaban (Eliquis®)</th>
<th>Dabigatran (Pradaxa®)</th>
<th>Edoxaban (Savaysa®)</th>
<th>Rivaroxaban (Xarelto®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard Dosing</strong></td>
<td>5 mg twice daily</td>
<td>150 mg twice daily</td>
<td>Determine renal function first</td>
<td>20 mg once daily with evening meal</td>
</tr>
<tr>
<td><strong>Renal Function Adjustments</strong></td>
<td>Reduce to 2.5 mg twice daily if SCr &gt; 2.5 mg/dL and age &gt; 80 years or weight &lt; 60 kg</td>
<td>Reduce to 75 mg twice daily if CrCl 15-30 mL/min</td>
<td>60 mg once daily if CrCl 50-95 mL/min Reduce to 30 mg once daily if CrCl 15-30 mL/min</td>
<td>Reduce to 15 mg once daily with evening meal if CrCl 15-50 mL/min</td>
</tr>
<tr>
<td><strong>Renal Function Contraindications</strong></td>
<td>None*</td>
<td>Avoid if CrCl &lt; 15 mL/min or receiving dialysis</td>
<td>Avoid if CrCl &gt; 95 mL/min or &lt; 15 mL/min</td>
<td>Avoid if CrCl &lt; 15 mL/min or receiving dialysis</td>
</tr>
</tbody>
</table>

CrCl creatinine clearance, DOAC direct-acting oral anticoagulant, NVAF non-valvular atrial fibrillation, SCr serum creatinine

*Safety in end-stage renal disease and hemodialysis limited to small studies
# Notable DOAC Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp inducers</td>
<td>Barbiturates, phenytoin, carbamazepine, rifampin, St. John's wort</td>
<td>Avoid dabigatran and edoxaban</td>
</tr>
<tr>
<td>P-gp inhibitors</td>
<td><strong>Amiodarone, dronedarone</strong>, diltiazem, verapamil, clarithromycin, grapefruit juice, cyclosporine, tacrolimus, ketoconazole*, itraconazole, ritonavir</td>
<td>Use dabigatran and edoxaban with caution; consider avoiding in renal dysfunction</td>
</tr>
<tr>
<td>P-gp plus strong CYP3A4 inducers</td>
<td>Barbiturates, phenytoin, carbamazepine, rifampin, St. John's wort</td>
<td>Avoid apixaban and rivaroxaban</td>
</tr>
<tr>
<td>P-gp plus strong CYP3A4 inhibitors</td>
<td>Clarithromycin, grapefruit juice, ketoconazole, itraconazole, ritonavir</td>
<td>Avoid rivaroxaban&lt;br&gt;Dose-reduce apixaban, or avoid if already using lower dose</td>
</tr>
<tr>
<td>P-gp plus moderate CYP3A4 inhibitors</td>
<td><strong>Dronedarone, diltiazem, verapamil</strong>, azithromycin</td>
<td>Use rivaroxaban with caution, especially in renal dysfunction</td>
</tr>
</tbody>
</table>

*Dose-reduce dabigatran or avoid in coexisting renal dysfunction. DOAC direct-acting oral anticoagulant, P-gp p-glycoprotein
NVAF Dose-Adjustment Recap

Renal Function

- Ensure doses are distinguished from other indications
- Safe in mild to moderate renal impairment when adjusted appropriately
- Apixaban *may* be safe in hemodialysis; avoid other DOACs in this population

Drug-Drug Interactions

- Avoid agents with strong drug-drug interactions (switch to alternative DOAC or to warfarin)
- Management of moderate drug-drug interactions should be individualized
Periprocedural Interruptions of DOAC Therapy

No clinically important risk

Low

Uncertain, Moderate, or High

Increased Baseline Bleeding Risk?

Yes for any of the following:
• Major bleed or ICH < 3 months
• Platelet abnormality (including concurrent aspirin use)
• Prior bleed during bridging

No

Do not interrupt. Time at DOAC trough if possible

Interrupt based on CrCl (see table on next slide)

Use clinical judgment. Interrupt by at least as long as determined by CrCl (see table).

CrCl creatinine clearance, DOAC direct-acting oral anticoagulant, ICH intracranial hemorrhage
Adapted from *J Am Coll Cardiol.* 2017 Feb 21;69(7):871-898.
Periprocedural Holding Recommendations

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Dabigatran</th>
<th>Apixaban, Edoxaban, or Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 80</td>
<td>≥ 30</td>
</tr>
<tr>
<td></td>
<td>50-79</td>
<td>15-29</td>
</tr>
<tr>
<td></td>
<td>30-49</td>
<td>&lt; 15</td>
</tr>
<tr>
<td></td>
<td>15-29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt; 15</td>
<td></td>
</tr>
</tbody>
</table>

**Low Bleeding Risk**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban, Edoxaban, or Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td>≥ 24 h</td>
<td>≥ 24 h</td>
</tr>
<tr>
<td>50-79</td>
<td>≥ 36 h</td>
<td>≥ 36 h</td>
</tr>
<tr>
<td>30-49</td>
<td>≥ 48 h</td>
<td>≥ 48 h</td>
</tr>
<tr>
<td>15-29</td>
<td>≥ 72 h</td>
<td>Consider anti-Xa and/or holding ≥ 48 h*</td>
</tr>
<tr>
<td>&lt; 15</td>
<td>Consider dTT and/or holding ≥ 96 h*</td>
<td>Consider anti-Xa and/or holding ≥ 48 h*</td>
</tr>
</tbody>
</table>

**Uncertain, Moderate, or High Bleeding Risk**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran</th>
<th>Apixaban, Edoxaban, or Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80</td>
<td>≥ 48 h</td>
<td>≥ 48 h</td>
</tr>
<tr>
<td>50-79</td>
<td>≥ 72 h</td>
<td>Consider dTT*</td>
</tr>
<tr>
<td>30-49</td>
<td>≥ 96 h</td>
<td>Consider anti-Xa and/or holding ≥ 48 h*</td>
</tr>
<tr>
<td>15-29</td>
<td>≥ 120 h</td>
<td></td>
</tr>
<tr>
<td>&lt; 15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*No data in these scenarios. CrCl creatinine clearance, DOAC direct-acting oral anticoagulant, dTT dilute thrombin time
Adapted from *J Am Coll Cardiol*. 2017 Feb 21;69(7):871-898.
Restarting DOAC Therapy Post-Procedure*

Complete hemostasis achieved with no bleeding complications, no high-risk features for bleeding, and no potentially catastrophic bleed location?

No

Low Post-Procedural Bleeding Risk

Re-initiate DOAC within 24 hours of the procedure.*

Consider temporary use of parenteral agent if unable to tolerate oral medications.

High Post-Procedural Bleeding Risk

Re-initiate DOAC within 48-72 hours after procedure.

Consider temporary use of parenteral agent if unable to tolerate oral medications.

Yes

Use clinical judgement.

CrCl creatinine clearance, DOAC direct-acting oral anticoagulant, ICH intracranial hemorrhage
Adapted from *J Am Coll Cardiol. 2017 Feb 21;69(7):871-898.*
Older Patients

- Outcomes in randomized trials are comparable in older subgroups
- Observational trials indicate similar results among “real-world” patients
- Excess extracranial bleeding with dabigatran in patients aged > 80 years
- Data do not support empiric dose-reductions in older patients

## Special Considerations Regarding Administration

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects of Food</strong></td>
<td>• Rivaroxaban &gt; 10 mg should be taken with a meal (dinner/largest meal of the day)</td>
</tr>
<tr>
<td></td>
<td>• Other DOACs may be taken without regard to food</td>
</tr>
<tr>
<td><strong>Crushing</strong></td>
<td>• Dabigatran capsules may not be crushed or opened</td>
</tr>
<tr>
<td></td>
<td>• Apixaban and rivaroxaban may be crushed and diluted for administration via feeding tube</td>
</tr>
<tr>
<td></td>
<td>• No data on edoxaban</td>
</tr>
<tr>
<td><strong>Dosing/Adherence</strong></td>
<td>• Edoxaban and rivaroxaban dosed once daily</td>
</tr>
<tr>
<td></td>
<td>• Apixaban and dabigatran dosed twice daily</td>
</tr>
</tbody>
</table>
Patient Case

You must develop an anticoagulation plan for a 72 year-old woman with newly diagnosed atrial fibrillation. She also has HFpEF, HTN, CKD, and hypothyroidism. She weighs 68 kg and has a SCr of 2.2 mg/dL (CrCl 25 mL/min). All other labs are within normal limits.

Which of the following would be an appropriate DOAC regimen? Select all that apply.

A. Apixaban 5 mg twice daily
B. Dabigatran 150 mg twice daily
C. Edoxaban 60 mg once daily
D. Rivaroxaban 15 mg daily with evening meal

Home Medications
- Diltiazem 120 mg daily (new)
- Lisinopril/HCTZ 20/25 mg daily
- Levothyroxine 88 mcg daily
Patient Case

You must develop an anticoagulation plan for a 72 year-old woman with newly diagnosed atrial fibrillation. She also has HFpEF, HTN, CKD, and hypothyroidism. She weighs 68 kg and has a SCr of 2.2 mg/dL (CrCl 25 mL/min). All other labs are within normal limits.

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D. Rivaroxaban 15 mg daily with evening meal

Home Medications
- Diltiazem 120 mg daily (new)
- Lisinopril/HCTZ 20/25 mg daily
- Levothyroxine 88 mcg daily

CKD chronic kidney disease, CrCl creatinine clearance, DOAC direct-acting oral anticoagulant, HCTZ hydrochlorothiazide, HFpEF heart failure with preserved ejection fraction, HTN hypertension, SCr serum creatinine
Management of High Risk Patients

Toby C. Trujillo, Pharm.D., BCPS-AQ Cardiology, FAHA, FCCP
Associate Professor
University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences
Clinical Specialist – Anticoagulation/Cardiology
University of Colorado Hospital
Aurora, Colorado
Case

A 42-year-old morbidly obese woman (124 kg, BMI 47.0 kg/m²) is on indefinite anticoagulation with warfarin for a history of recurrent unprovoked VTE. She asks if she can switch to one of the “new” drugs. How do you advise her?

a. Switch to a DOAC – safer and more convenient than warfarin

b. Switch to apixaban – more effective than warfarin in patients of her size when weight-based dose is used

c. Do not switch – DOACs less effective than warfarin in patients of her size

d. Do not switch – paucity of evidence on DOAC use in patients of her size
DOACs in Patients with and Obesity
VTE Trial - Results in high body weight* subgroup

Recurrent VTE

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DOACs Events</th>
<th>DOACs Total</th>
<th>VKA Events</th>
<th>VKA Total</th>
<th>Weight</th>
<th>Risk Ratio Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY</td>
<td>11</td>
<td>509</td>
<td>18</td>
<td>508</td>
<td>18.3%</td>
<td>0.61 [0.29, 1.28]</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>11</td>
<td>491</td>
<td>11</td>
<td>486</td>
<td>14.7%</td>
<td>0.99 [0.43, 2.26]</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>13</td>
<td>683</td>
<td>10</td>
<td>672</td>
<td>15.0%</td>
<td>1.28 [0.56, 2.90]</td>
</tr>
<tr>
<td>HOKUSAI</td>
<td>22</td>
<td>611</td>
<td>23</td>
<td>654</td>
<td>30.5%</td>
<td>1.02 [0.58, 1.82]</td>
</tr>
<tr>
<td>RECOVER-I&amp;II</td>
<td>18</td>
<td>438</td>
<td>14</td>
<td>394</td>
<td>21.4%</td>
<td>1.16 [0.58, 2.29]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2732</strong></td>
<td><strong>2714</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.98 [0.72, 1.35]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>75</strong></td>
<td></td>
<td><strong>76</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 2.23, df = 4 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.10 (P = 0.92)

Bleeding, M+CRNM

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DOACs Events</th>
<th>DOACs Total</th>
<th>VKA Events</th>
<th>VKA Total</th>
<th>Weight</th>
<th>Risk Ratio Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPLIFY</td>
<td>1</td>
<td>521</td>
<td>10</td>
<td>518</td>
<td>2.8%</td>
<td>0.10 [0.01, 0.77]</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>31</td>
<td>488</td>
<td>39</td>
<td>481</td>
<td>27.9%</td>
<td>0.78 [0.50, 1.33]</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>68</td>
<td>683</td>
<td>61</td>
<td>670</td>
<td>35.7%</td>
<td>1.09 [0.79, 1.52]</td>
</tr>
<tr>
<td>HOKUSAI</td>
<td>54</td>
<td>611</td>
<td>54</td>
<td>654</td>
<td>33.6%</td>
<td>1.07 [0.75, 1.54]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2303</strong></td>
<td><strong>2323</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td></td>
<td><strong>0.93 [0.65, 1.32]</strong></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td><strong>154</strong></td>
<td></td>
<td><strong>164</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.06; Chi² = 6.46, df = 3 (P = 0.09); I² = 54%
Test for overall effect: Z = 0.43 (P = 0.67)

*Cut-off for defining high BW was 100 kg in 4 trials and 90 kg in 2 trials.

# PK/PD data

### Rivaroxaban 10 mg single dose study in healthy volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>70-80 kg (n=12)</th>
<th>&gt;120 kg (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng mL⁻¹ hr)</td>
<td>1029</td>
<td>1155</td>
</tr>
<tr>
<td>C_max (ng/mL)</td>
<td>143.4</td>
<td>149.0</td>
</tr>
<tr>
<td>t_{1/2} (hr)</td>
<td>7.2</td>
<td>7.3</td>
</tr>
</tbody>
</table>

### Apixaban 10 mg single dose study in healthy volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>65-85 kg (n=16)</th>
<th>&gt;120 kg (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng mL⁻¹ hr)</td>
<td>2024</td>
<td>1561</td>
</tr>
<tr>
<td>C_max (ng/mL)</td>
<td>207</td>
<td>144</td>
</tr>
<tr>
<td>t_{1/2} (hr)</td>
<td>12.0</td>
<td>8.8</td>
</tr>
</tbody>
</table>

FDA-approved DOAC labeling for VTE treatment in obesity

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Dosing for VTE in patients with obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>No dosage recommendation</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>No dosage recommendation</td>
</tr>
<tr>
<td>Apixaban</td>
<td>No dosage recommendation</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>No dosage recommendation</td>
</tr>
</tbody>
</table>
International Society on Thrombosis and Haemostasis recommendations

1. We suggest that DOACs should not be used in patients with a BMI > 40 kg/m² or a weight > 120 kg.

2. If a DOAC is used in a patient with a BMI > 40 kg/m² or a weight > 120 kg, we suggest checking a peak and trough drug level. If the level falls within the expected range, continuation of the DOAC seems reasonable. If the level is found to be below the expected range, we suggest changing to a VKA rather than adjusting the dose of the DOAC.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose, mg</th>
<th>Trough concentration, ng/mL</th>
<th>Peak concentration, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median</td>
<td>5th to 95th percentile</td>
</tr>
<tr>
<td>Dabigatran²</td>
<td>150 BID</td>
<td>90</td>
<td>31-225</td>
</tr>
<tr>
<td>Rivaroxaban³</td>
<td>20 daily</td>
<td>26</td>
<td>6-87</td>
</tr>
<tr>
<td>Apixaban⁴</td>
<td>5 BID</td>
<td>103</td>
<td>41-230</td>
</tr>
<tr>
<td>Edoxaban⁵</td>
<td>60 daily</td>
<td>22</td>
<td>10-40*</td>
</tr>
</tbody>
</table>

Case

A 42-year-old morbidly obese woman (124 kg, BMI 47.0 kg/m²) is on indefinite anticoagulation with warfarin for a history of recurrent unprovoked VTE. She asks if she can switch to one of the “new” drugs. How do you advise her?

a. Switch to a DOAC – safer and more convenient than warfarin

b. Switch to apixaban – more effective than warfarin in patients of her size when weight-based dose is used

c. Do not switch – DOACs less effective than warfarin in patients of her size

d. Do not switch – paucity of evidence on DOAC use in patients of her size
DOACs in Patients with Renal Insufficiency
VTE Treatment trials:
Results stratified by renal function

Recurrent VTE

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>30-49 ml/min</th>
<th>≥ 50 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>26/898 (2.9%)</td>
<td>39/891 (4.4%)</td>
</tr>
<tr>
<td></td>
<td>307/12248 (2.5%)</td>
<td>316/12262 (2.6%)</td>
</tr>
</tbody>
</table>

RR 0.51 (0.26-0.99)
RR 0.60 (0.40-0.90)
RR 0.70 (0.43-1.15)
RR 0.97 (0.83-1.14)

Major Bleeding

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>30-49 ml/min</th>
<th>≥ 50 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16/678 (1.8%)</td>
<td>33/870 (3.8%)</td>
</tr>
<tr>
<td></td>
<td>132/12329 (1.1%)</td>
<td>200/12358 (1.6%)</td>
</tr>
</tbody>
</table>

RR 0.51 (0.26-0.99)
RR 0.60 (0.40-0.90)

Similar results in Phase III non-valvular atrial fibrillation DOAC trials

<table>
<thead>
<tr>
<th>GFR</th>
<th>Stroke/Systemic Embolism RR (95% CI)</th>
<th>Major Bleeding RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-80 mL/min</td>
<td>0.71 (0.62-0.81)</td>
<td>0.88 (0.80-0.97)</td>
</tr>
<tr>
<td>&lt; 50 mL/min</td>
<td>0.79 (0.66-0.94)</td>
<td>0.80 (0.70-0.91)</td>
</tr>
</tbody>
</table>

FDA labeling Dialysis – Apixaban and Rivaroxaban

- **Apixaban**
  - Administration of apixaban in the usually recommended dose will result in concentrations of apixaban and PD activity similar to the Aristotle trial...
  - Systemic exposure to a **single** 5 mg dose in ESRD after a 4 hours hemodialysis session in 36% higher when compared to subjects with normal renal function

- **Rivaroxaban**
  - Administration of rivaroxaban 15 mg once daily will result in rivaroxaban concentrations of rivaroxaban and pharmacodynamics activity similar to ROCKET AF trial...
  - Systemic exposure to rivaroxaban in a **single** 15 mg dose in ESRD after a 4 hour hemodialysis session was 56% higher when compared to subjects with normal renal function

Xarelto (rivaroxaban) prescribing information. 
Eliquis (apixaban) prescribing information.
Dose-Finding Study of Rivaroxaban in Hemodialysis Patients

An S. De Vriese, MD, PhD,1 Rogier Caluwé, MD,2 Els Bailleul, MD,3
Dirk De Bacquer, PhD,4 Daniëlle Borrey, PhD,5 Bruno Van Vlem, MD, PhD,2
Stefaan J. Vandecasteele, MD, PhD,1 and Jan Emmerechts, MD, PhD5

Background: Use of vitamin K antagonists for the prevention of stroke and systemic embolism in dialysis patients with nonvalvular atrial fibrillation is controversial. However, no good alternatives presently are available. The anti–factor Xa antagonist rivaroxaban is contraindicated for lack of pharmacokinetic, pharmacodynamic, and clinical data. This study aims to characterize the pharmacokinetics/pharmacodynamics of rivaroxaban in maintenance hemodialysis patients.

Study Design: Pharmacokinetic and pharmacodynamic study.

Setting & Participants: 18 maintenance hemodialysis patients without residual kidney function at 2 centers.

Drug Administration, Outcomes, & Measurements: (1) A single dose of 10 mg of rivaroxaban was administered at the end of each of 3 consecutive dialysis sessions and area under the curve (AUC) and the effect on coagulation parameters were measured for 44 hours thereafter. (2) A single dose of 10 mg of rivaroxaban was given 6 to 8 hours before a dialysis session and the effect of dialysis on rivaroxaban concentrations was evaluated. (3) To assess potential accumulation, 10 mg of rivaroxaban was given once daily and AUC was measured during 24 hours on days 1 and 7.

Results: Mean AUC0-44 of rivaroxaban plasma concentrations after a single dose of 10 mg was 2,072 µg/Lh, mean maximum concentration was 172.6 µg/L, and mean terminal elimination half-life was 8.6 hours. Dialysis had no appreciable effect on rivaroxaban plasma concentrations. Mean trough concentration after multiple daily doses of 10 mg was 20.2 µg/L.

Limitations: Higher rivaroxaban doses and patients with substantial residual kidney function were not studied.

Conclusions: A 10-mg dose of rivaroxaban in hemodialysis patients without residual kidney function results in drug exposure similar as published for 20 mg in healthy volunteers. Rivaroxaban is not eliminated by dialysis. There is no accumulation after multiple daily dosing. The efficacy and safety of rivaroxaban in hemodialysis patients should be the subject of a large randomized trial.

Am J Kidney Dis. 66(1):91-98. © 2015 by the National Kidney Foundation, Inc.
Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients

Thomas A. Mavrakanas,*† Caroline F. Samer,‡ Sharon J. Nessim,* Gershon Frisch,* and Mark L. Lipman*

*Division of Nephrology, Jewish General Hospital, McGill University, Montreal, Quebec, Canada; and †Division of General Internal Medicine and ‡Department of Clinical Pharmacology and Toxicology, Geneva University Hospitals, Geneva, Switzerland


Figure 4. Schematic presentation of study interventions (phases 1–3). Phase 1: apixaban exposure after a 2.5 mg single dose and at steady state (day 8). Phase 2: effect of hemodialysis on apixaban concentration at steady state. Phase 3: apixaban exposure at steady state with a 5 mg bid dose. Bid, twice daily.
Apixaban Dose Response at Steady State

Peak levels (ng/ml) with 2.5 and 5 mg bid

Cmax – Healthy volunteers on 5 mg BID 128.5 ng/ml

Cmax – 131.5 ng/ml

Cmax – 307 ng/ml

VTE in Cancer
Guideline Recommendations for Treatment of DVT/PE

- In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2C), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C) or edoxaban (Grade 2C).

- In patients with DVT of the leg or PE who receive extended therapy, we suggest that there is no need to change the choice of anticoagulant after the first 3 months (Grade 2C).
LMWH vs VKA for VTE in Cancer

**Recurrent VTE**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>LMWH Events</th>
<th>LMWH Total</th>
<th>VKA Events</th>
<th>VKA Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer et al. 2002 (CANTHANOX)</td>
<td>2</td>
<td>67</td>
<td>3</td>
<td>71</td>
<td>2.5%</td>
<td>0.71 [0.12, 4.10]</td>
</tr>
<tr>
<td>Lee 2003 et al. (CLOT)</td>
<td>27</td>
<td>336</td>
<td>53</td>
<td>336</td>
<td>39.9%</td>
<td>0.51 [0.33, 0.79]</td>
</tr>
<tr>
<td>Deitcher et al. 2006 (ONCENOX)</td>
<td>4</td>
<td>53</td>
<td>3</td>
<td>32</td>
<td>3.7%</td>
<td>0.81 [0.19, 3.37]</td>
</tr>
<tr>
<td>Hull et al. 2006 (Main-LITE)</td>
<td>7</td>
<td>99</td>
<td>16</td>
<td>99</td>
<td>10.8%</td>
<td>0.44 [0.19, 1.02]</td>
</tr>
<tr>
<td>Romera et al. 2009</td>
<td>2</td>
<td>36</td>
<td>7</td>
<td>33</td>
<td>3.4%</td>
<td>0.26 [0.06, 1.17]</td>
</tr>
<tr>
<td>Lee 2015 et al. (CATCH)</td>
<td>31</td>
<td>449</td>
<td>45</td>
<td>451</td>
<td>39.8%</td>
<td>0.69 [0.45, 1.07]</td>
</tr>
</tbody>
</table>

Total (95% CI) 1040 1022 100.0% 0.57 [0.43, 0.75]

Total events 73 127
Heterogeneity: Tau² = 0.00; Chi² = 2.70, df = 5 (P = 0.75); I² = 0%
Test for overall effect: Z = 4.01 (P < 0.0001)

**Major Bleeding**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>LMWH Events</th>
<th>LMWH Total</th>
<th>VKA Events</th>
<th>VKA Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meyer et al. 2002 (CANTHANOX)</td>
<td>5</td>
<td>67</td>
<td>12</td>
<td>71</td>
<td>19.5%</td>
<td>0.44 [0.16, 1.19]</td>
</tr>
<tr>
<td>Lee 2003 et al. (CLOT)</td>
<td>19</td>
<td>336</td>
<td>12</td>
<td>333</td>
<td>30.3%</td>
<td>1.57 [0.77, 3.18]</td>
</tr>
<tr>
<td>Deitcher et al. 2006 (ONCENOX)</td>
<td>6</td>
<td>53</td>
<td>1</td>
<td>32</td>
<td>5.6%</td>
<td>3.62 [0.46, 28.74]</td>
</tr>
<tr>
<td>Hull et al. 2006 (Main-LITE)</td>
<td>7</td>
<td>100</td>
<td>7</td>
<td>100</td>
<td>18.9%</td>
<td>1.00 [0.36, 2.75]</td>
</tr>
<tr>
<td>Lee 2015 et al. (CATCH)</td>
<td>12</td>
<td>449</td>
<td>11</td>
<td>451</td>
<td>25.7%</td>
<td>1.10 [0.49, 2.46]</td>
</tr>
</tbody>
</table>

Total (95% CI) 1005 987 100.0% 1.08 [0.65, 1.79]

Total events 49 43
Heterogeneity: Tau² = 0.09; Chi² = 5.56, df = 4 (P = 0.23); I² = 28%
Test for overall effect: Z = 0.28 (P = 0.78)
Phase 3 VTE trials DOACS - Patients with Active Cancer

Primary Efficacy Endpoint

None of these comparisons are statistically significant

TSOA = target specific oral anticoagulant

### Hokusai - VTE
- Randomized, open-label, non-inferiority trial
- Acute, symptomatic VTE in cancer patients
  - 525 patients dalteparin (200 units/kg daily)
  - 525 patients edoxaban (LMWH lead in, 60 mg daily)
- Primary outcome (first recurrent VTE or major bleeding event over 12 months)
  - Dalteparin: 12.7%
  - Edoxaban: 13.5%
  - Statistically significant for non-inferiority

### Select – D Pilot Trial
- Randomized, open-label, pilot trial
- Acute, symptomatic VTE in cancer patients
  - 203 patients dalteparin (200 units/kg daily)
  - 203 patients rivaroxaban (15 mg BID x 21 days, then 20 mg daily)
- Primary outcome (first recurrent VTE over 6 months)
  - Dalteparin: 11%
  - Rivaroxaban: 4%
  - Confidence intervals overlap, NS despite large difference
Drug Interactions with DOACs
DOAC Drug Interaction Potential

- **Dabigatran – IIa inhibitor**
  - Esterase-mediated hydrolysis when absorbed
  - Absorption dependent on P-glycoprotein
  - Minimal (20%) hepatic metabolism – not CYP3A4
  - Approximately 80% renal elimination

- **Rivaroxaban – Xa inhibitor**
  - Absorption dependent on P-glycoprotein
  - Approximately 65% metabolized by hepatic CYP3A4 and CYP2J3
  - Approximately 35% renal elimination

- **Apixaban – Xa inhibitor**
  - Absorption dependent on P-glycoprotein
  - Approximately 73% metabolized by hepatic CYP3A4
  - Approximately 27% renal elimination

- **Edoxaban – Xa inhibitor**
  - Absorption dependent on P-glycoprotein
  - Approximately 50% hepatic metabolism, but only 4% CYP3A4
  - Approximately 50% renal elimination

P-Glycoprotein (P-gp): A Drug Transport Protein

- Present in liver, kidney, brain, capillaries, placenta, and GI tract
- Functions as an “efflux pump” to prevent absorption of certain drugs that are P-gp “substrates”

Mechanism of P-Glycoprotein Drug Interactions

- Drugs that inhibit P-gp will increase absorption of a substrate, increasing its serum concentrations.
- Drugs that induce P-gp will decrease absorption of a substrate, reducing its serum concentrations.

# Dabigatran Drug Interactions

<table>
<thead>
<tr>
<th>Mechanism- Interacting Medication</th>
<th>Effect – Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp induction</td>
<td></td>
</tr>
<tr>
<td>rifampin</td>
<td>↑stroke risk, avoid combination</td>
</tr>
<tr>
<td>P-gp inhibition with CrCl 30 – 50 mL/min</td>
<td></td>
</tr>
<tr>
<td>ketoconazole, dronedarone</td>
<td>↑bleeding risk, consider dose reduction to 75 mg BID</td>
</tr>
<tr>
<td>P-gp inhibition with CrCl 15 – 30 mL/min</td>
<td></td>
</tr>
<tr>
<td>amiodarone, verapamil, ketoconazole, dronedarone, diltiazem, clarithromycin</td>
<td>↑bleeding risk, avoid combination</td>
</tr>
<tr>
<td>Pharmacodynamic interaction</td>
<td></td>
</tr>
<tr>
<td>aspirin, clopidogrel, NSAIDs</td>
<td>↑bleeding risk, assess risks and benefits</td>
</tr>
</tbody>
</table>

Pradaxa (dabigatran etexilate mesylate) prescribing information. 2017 Nov.
# Rivaroxaban Drug Interactions

<table>
<thead>
<tr>
<th>Mechanism- Interacting Medication</th>
<th>Effect – Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong dual CYP 3A4 &amp; P-gp induction</td>
<td></td>
</tr>
<tr>
<td><em>rifampin, phenytoin, carbamazepine, St. John’s wort</em></td>
<td>↑stroke risk, avoid combination</td>
</tr>
<tr>
<td>Strong dual CYP 3A4 &amp; P-gp inhibition</td>
<td></td>
</tr>
<tr>
<td><em>conivaptan, HIV protease inhibitors, itraconazole, ketoconazole</em></td>
<td>↑bleeding risk, avoid combination</td>
</tr>
<tr>
<td>Weak to moderate CYP 3A4 &amp; P-gp inhibition &amp; CrCl 15-80 mL/min</td>
<td></td>
</tr>
<tr>
<td><em>amiodarone, verapamil, diltiazem, erythromycin, dronedarone, cimetidine</em></td>
<td>↑bleeding risk, avoid combination unless benefit exceeds risk, concurrent administration was allowed in ROCKET-AF Trial</td>
</tr>
<tr>
<td>Pharmacodynamic interaction</td>
<td></td>
</tr>
<tr>
<td><em>aspirin, clopidogrel, NSAIDs</em></td>
<td>↑bleeding risk, assess risks and benefits</td>
</tr>
</tbody>
</table>

Xarelto (rivaroxaban) prescribing information. 2017 Nov
## Apixaban Drug Interactions

<table>
<thead>
<tr>
<th>Mechanism- Interacting Medication</th>
<th>Effect – Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong dual CYP 3A4 &amp; P-gp induction</strong></td>
<td></td>
</tr>
<tr>
<td>rifampin, phenytoin, carbamazepine, St. John’s wort</td>
<td>↑stroke risk, avoid combination</td>
</tr>
<tr>
<td><strong>Strong dual CYP 3A4 &amp; P-gp inhibition</strong></td>
<td></td>
</tr>
</tbody>
</table>
| itraconazole, ketoconazole, ritonavir, clarithromycin | • If on 2.5 mg BID: ↑bleeding risk, avoid combination  
• If on > 2.5 mg BID: ↑bleeding risk, reduce dose by 50% |
| **Pharmacodynamic interaction** | |
| aspirin, clopidogrel, NSAIDs | ↑bleeding risk, assess risks and benefits |

Eliquis (apixaban) prescribing information. 2017 Nov.
# Edoxaban Drug Interactions

<table>
<thead>
<tr>
<th>Mechanism- Interacting Medication</th>
<th>Effect – Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp induction</td>
<td></td>
</tr>
<tr>
<td>rifampin</td>
<td>↑ stroke risk, avoid combination</td>
</tr>
<tr>
<td>P-gp inhibition- atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No dose reductions; dose reduction in those on P-gp inhibitors in trial resulted in lower than expected concentrations</td>
</tr>
<tr>
<td>P-gp inhibition- VTE</td>
<td></td>
</tr>
<tr>
<td>verapamil, quinidine, azithromycin, clarithromycin, erythromycin, itraconazole, ketoconazole</td>
<td>↑ bleeding risk, reduce dose to 30 mg daily; adjust dose upward after short term P-gp inhibitor administration if no other indication for dose decrease present</td>
</tr>
<tr>
<td>Pharmacodynamic interaction</td>
<td></td>
</tr>
<tr>
<td>aspirin, clopidogrel, NSAIDs</td>
<td>↑ bleeding risk, assess risks and benefits</td>
</tr>
</tbody>
</table>

Savaysa (edoxaban) prescribing information. 2017 Nov.
## P-Glycoprotein Drug Interactions

**Inducers**
- clotrimazole
- St. John’s wort
- midazolam
- nifedipine
- phenobarbital
- phenytoin
- rifampin

**Inhibitors**
- amiodarone
- cefoperazone
- ceftriaxone
- clarithromycin
- cyclosporine
- diltiazem
- dipyridamole
- erythromycin
- hydrocortisone
- itraconazole
- ketoconazole
- nicardipine
- nifedipine
- propranolol
- quinidine
- quinine
- tacrolimus
- tamoxifen
- verapamil
# CYP3A4 Drug Interactions

**Inducers**
- carbamazepine
- efavirenz
- glucocorticoids
- nevirapine
- phenobarbital
- phenytoin
- primidone
- rifampin
- rifapentine
- ritonavir
- St. John’s wort

**Inhibitors**
- amiodarone
- amprenavir
- aprepitant
- atazanavir
- cimetidine
- clarithromycin
- cyclosporine
- diltiazem
- erythromycin
- fluconazole
- fluoxetine
- fluvoxamine
- grapefruit juice
- indinavir
- itraconazole
- ketoconazole
- lopinavir
- nefazodone
- nelfinavir
- quinidine
- quinupristin and dalfopristin
- ritonavir
- saquinavir
- verapamil
- voriconazole
Adherence to and Persistent with DOACs

Brent N. Reed, PharmD, BCPS-AQ Cardiology, FAHA
Associate Professor
University of Maryland School of Pharmacy
Clinical Specialist – Advanced Heart Failure
University of Maryland Medical Center
Baltimore, MD
Patient Case

A 62 year-old man with atrial fibrillation reports being dissatisfied with the meal planning necessary to maintain a therapeutic INR on warfarin and would like to try a DOAC. With a few exceptions, the patient is usually therapeutic each month. The physician with whom you practice is usually reluctant to transition patients who are stable on warfarin.

With respect to adherence/persistence, which of the following could you use to justify this change? Select all that apply.

A. Adherence is higher with DOAC therapy compared to warfarin.
B. Adherence can be enhanced with pharmacist-led monitoring of DOAC therapy.
C. Adherence is higher with once vs. twice daily DOAC therapy.
D. Adherence is associated with lower risks of thromboembolic events and death.

CKD chronic kidney disease, CrCl creatinine clearance, DOAC direct-acting oral anticoagulant, HCTZ hydrochlorothiazide, HFpEF heart failure with preserved ejection fraction, HTN hypertension, SCr serum creatinine
Terminology

Adherence
Degree to which a patient adheres to the recommended treatment regimen. Example of non-adherence: running out of a medication for a few days before getting it refilled.

Persistence
Continuation for the full intended duration of treatment (which may differ by indication). Example of non-persistence: permanently discontinuing prior to a 3-month duration for provoked VTE.
Impact of Early Non-Persistence in NVAF

<table>
<thead>
<tr>
<th>Drug/Outcome</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dabigatran</strong></td>
<td></td>
</tr>
<tr>
<td>Composite outcome</td>
<td>1.76 (1.60 – 1.94)</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>3.75 (2.59 – 5.43)</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td></td>
</tr>
<tr>
<td>Composite outcome</td>
<td>1.89 (1.64 – 2.19)</td>
</tr>
<tr>
<td>Cerebrovascular event</td>
<td>6.25 (3.37 – 11.58)</td>
</tr>
</tbody>
</table>

CI confidence interval, NVAF non-valvular atrial fibrillation
DOAC Persistence Rates

Discontinuation Rates in Major NVAF Trials¹

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Discontinuation Rate</th>
<th>ADR-Related Discontinuation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>25.3%</td>
<td>3.0%</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>21.9%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>34.4%</td>
<td>4.0%</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>25.3%</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

Additionally, observational studies show adherence/persistence rates as good or better than warfarin (≥ 70% vs. 40-65%).¹²

DOAC direct-acting oral anticoagulant, NVAF non-valvular atrial fibrillation
No single DOAC is consistently better although adherence to apixaban and rivaroxaban tends to be higher than with dabigatran.

DOAC direct-acting oral anticoagulant

Nonadherence Causes & Contributors

Patient Factors

Provider / System Factors

Modifiable vs. Non-modifiable
“Antithrombotic therapy should be individualized based on shared decision-making...”
(Class I, Level of Evidence C)¹

Perceptions regarding the extent to which decisions are shared between patients and providers do not match.²³

---

Patient Factors

Non-Modifiable

- Demographics (e.g., age, gender)
- Socioeconomic status
- Treatment experience
- Comorbidities
- Medication complexity (inverse U-shaped curve)

Modifiable

- Capability (e.g., patient understanding, ability to manage disease)
- Motivation (e.g., perceived risks and benefits of therapy)
- Social determinants of health (e.g., medication access)

Prescribers tend to overestimate the risk of bleeding and prioritize it over the risk of stroke.\textsuperscript{1,2}

Prescribers may favor warfarin over DOACs due to:
- Perceptions regarding adherence\textsuperscript{3}
- Comfort (especially in high-risk subgroups)
- Fewer barriers to prescribing

DOACs direct-acting oral anticoagulants

Strategies to Improve Adherence/Persistence

- Patient-individualized education at initiation and at each visit/refill
- Routine contact/monitoring for adherence and adverse effects
- Addressing barriers to access (e.g., cost, formulary coverage)
- Individualizing therapy to coincide with patient preferences and medication-taking behaviors
- Increasing prescribing via clinician education and decision-support
- Developing health technology infrastructure to support adherence tracking and reporting

Patient Case

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C. Adherence is higher with once vs. twice daily DOAC therapy.
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CKD chronic kidney disease, CrCl creatinine clearance, DOAC direct-acting oral anticoagulant, HCTZ hydrochlorothiazide, HFpEF heart failure with preserved ejection fraction, HTN hypertension, SCr serum creatinine
Assessment Question 1

Which of the following would be an appropriate once-daily option in a patient with atrial fibrillation and normal renal function (creatinine clearance $\geq 120$ mL/min)?

A. Apixaban
B. Dabigatran
C. Edoxaban
D. Rivaroxaban
Assessment Question 2

Which of the following is a modifiable patient-related barrier to adherence/persistence?

A. Socioeconomic status
B. Perceived benefits of therapy
C. Experience with treatment
D. Comorbid diseases/conditions
Assessment Question 3

Which of the following statements is true regarding the use of direct oral anticoagulants in the treatment of VTE?

A. Patients with a provoked proximal DVT or PE and at high risk of bleeding should receive extended anticoagulation to prevent recurrence

B. Patients receiving edoxaban for the management of DVT or PE should first receive 7 days of low molecular weight heparin therapy

C. Patients receiving apixaban for the management of DVT or PE should first receive 7 days of low molecular weight heparin therapy

D. Patients with a provoked proximal DVT or PE should receive anticoagulation for a minimum of 6 months
Assessment Question 4

Which of the following statements is true regarding the use of direct oral anticoagulants (DOACs)?

A. Patients who weigh > 100 kg should not be managed with DOACs

B. Compared to dalteparin, the use of rivaroxaban resulted in a lower rate of recurrent VTE in patients being treated for an acute VTE in the setting of cancer.

C. Patients with atrial fibrillation and receiving rivaroxaban along with concomitant therapy with phenytoin should have their dose increased to 15 mg BID

D. Patients on hemodialysis receiving apixaban 5 mg BID experience similar plasma drug concentrations as patient with normal renal function
Direct Oral Anticoagulants: Determining Proper Use and Dose

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Clinical Specialist – Advanced Heart Failure
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